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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,655	04/27/2001	Wei Huang	LJL 357	9013

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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,655	HUANG ET AL.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *94-105 and 108-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *94-101,108,110 and 112-115* is/are rejected.

7)☒ Claim(s) *102-105, 109, 111* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and Affidavit under Rule 1.132 filed on 4/8/2004 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claims 1-93, 106, 107 are cancelled.
2. Claims 94-105, 108-115 are currently under examination.

Claim Rejections - 35 USC § 112

Scope of Enablement

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 94 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detect phosphate modification, does not reasonably provide enablement for any enzymatic modification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The current invention directs to a method to detect the activity of an enzyme that operates on a substrate to form a product detectable by use of luminescence polarization. Applicant recites in the main independent claim that the said method is capable of detecting the activity of an enzyme that operate on a substrate to form a product in a sample. (claim 94) However, (1) in Remarks and Arguments applicant admits that the instant invention relates to phosphorylation modification (See page 12, illustration); (2) applicant indicates that the invention directs to phosphate modification (page 22, second paragraph); and (3) the enzymes involved including kinases, phosphatases,

phosphodiesterases, and cyclases which are phosphate related enzymes. (page 24, second paragraph) Nowhere in the specification teaches that other enzymatic modifiation, such as hydroxylation of proline and lysine residues to form the hydroxyproline and hydroxylysine residues in collagen; carboxylation of glutamate to .gamma.-carboxyglutamate; methylation, acetylation or phosphorylation of the .epsilon.-amino group of lysine; glycosylation; and the attachment of prosthetic groups, e.g., the attachment of carbohydrates to glycoproteins. Accordingly, the instant invention relates to a method of detecting enzymatic phosphorylation on a substrate, not *any* enzymatic modification on a substrate.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 94-101, 108, 110, 112-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nikiforov (USP 6472141) in view of Posewits et al. (Anal. Chem. 1999, Vol. 7: 2883-2892).

Nikiforov teaches a fluorescence polarization assay to determine the enzymatic operation of a phosphoryatable compound, i.e. activity of phosphotase (dephosphorylate) or kinase (phosphorylate) on the polypeptide substrate. (Col. 3, line 7-20) Nikiforov teaches the steps of conducting the assay includes, first contacting the substrate with the enzyme, then adding a second mixture binding molecule, i.e. proteins (macromolecule) containing metal ion selected from Fe3+, Ca2+, Ni2+ and Zn2+, and detecting the difference of luminescence polarization emitted from the sample. (supra; Col. 7, line 15-27) Nikiforov teaches that the bound fluorescent molecules show higher fluorescent polarization compared to the unbound molecules, and there is no need of separation of the unbound from the bound molecules for calculation. (supra and the equation (2)) Nikiforov teaches that the product can be flourescently labeled, i.e. luminescent. (claim 18) It is inherent that the phosphorylatable compounds taught by Nikiforov are products of posttranslational modification in the biological system. The binding molecule taught by Nikiforov, e.g. protein, could be viewed as a nanoparticle. *Supra*. The method taught by Nikiforov also can be applied for screening inhibitors or enhancers of the enzymes. (Col. 7, lines 36-40) Nikiforov also teaches high-throughput, i.e. mass sample array, for the fluorescent polarization method. (Col. 21, line 17-22; Col. 24, line 18-20; Col. 25, line 3-6) However, Nikiforov does not specifically teach using gallium (Ga) metal ion for its fluorescent polarization assay.

Posewitz et al teach using gallium (Ga) rendering more selective and efficient results over the choice of Fe3+, or Al3+ in purification of phospopetides molecule. (See Abstract, and page 2892, Left Col. Second paragraph) Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to replace the conventional metal ions of Fe3+, or Al3+ for capturing phosphopeptides as taught by Nikiforov with the Ga ion as taught by Posewitz et al. with a reasonable expectation of success. The motivation to do so would have been the recognition of the following: (1) Fe3+ and Ga ion have been recognized possessing similar behavior in the ion binding proteins (Posewitz et al. reference, page 2892, Right Column, first paragraph;

Figure 3); (2) Ga ion may substitute Fe3+ in study ion binding protein mechanism, supra; (3) Ga ion has been shown more selective and efficient metal ion for targeting phosphopeptides. *Supra.*

With respect to claim 113, where the recited binding coefficient is no longer than about 10^{-8} M which is a general binding kinetic parameter indicating specific binding . It would have been obvious to one having ordinary skill in the art at the time the invention was made to optimize the binding assay, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

Allowable Subject Matter

6. Claims 102-105, 109, 111 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: The closest prior arts taught by Nikiforov and Posewits et al. as discussed supra disclose a fluorescence polarization assay to determine the enzymatic activity of an enzyme operating on a substrate by use of a metal ion, e.g. Gallium. Both Nikiforov and Posewits et al. teach using this method on kinase and phosphotase, but not on phosphodiesterase as recited in this application. Furthermore, the substrate for the phosphodiesterase is nucleotide, which is chemically and biologically distinct from the polypeptides used in both Nikiforov and Posewits' reference. Therefore, prior arts neither teach nor suggest use fluorescence polarization coupling with the Gallium ion to determine the activity of phosphodiesterase.

Response to Applicant's Arguments

7. The rejections of claims 94-101, 108, 110, 112-115 under 35 U.S.C. 103(a) as being unpatentable over Nikiforov in view of Posewits et al., are maintained.

Applicant's main arguments center on the secondary reference, i.e. Posewits et al., or the unexpected *benefit* to use Ga instead of Fe in fluorescence polarization detection of the target molecules. Applicant asserts that (1) using Ga results in an enhanced intensity, (100-fold) instead of quenching intensity; (2) Ga provides greater dynamic range of polarization; and (3) Ga provides better distinguish the existence of product in a mixture of substrate and product. Applicant also presents the data of comparison the effects of Ga and Fe on total fluorescence intensities. (See Remarks, page 11 and Declaration Figure 1)

Applicant's arguments have been considered but are not persuasive. Posewits et al. reference teaches using Ga as a binding partner for phosphopeptide. In fact, Posewits et al. disclose that one skilled in the art often substitutes iron with Ga to study protein binding phenomena, and comments that "[I]*t is therefore not surprising that it (Ga) mimics the proven ability of Fe to bind phosphorylated peptides. In addition, Ga must possesses certain unique features to providing more selective retention of phosphorylated peptides."* (See page 2892, right column, first paragraph) Thus, replacing iron with Ga is within routine skilled in the art in studying the analogous art, such as phosphopeptides binding. The substitution of iron with Ga leads to a better result would not be "surprising" since Ga has been shown possesses a "unique" feature in terms of binding to the phosphopeptides compared to iron.

As indicated in the Office Action that Nikiforov reference teaches using *Fe*, Al, Ni, Ca polycationic component as the binding partners bound to the phosphorylated product for polarization fluorescence assay. (See claims 1, 8, 12, 13) It would have been obvious to one having ordinary skill in the art at the time the invention was made to have provided Nikiforov with the Ga metal to as an alternative metal other than iron because using Ga substituting iron in studying phosphopeptide binding is known in the art and the results would be better is also expected due to the unique feature of Ga in binding to phosphopeptides as revealed by Posewits et al.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-282-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641

June 1, 2004

LONG V. LE
SUPERVISORY PATENT EXAMINER
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06/01/04